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Enantioselective synthesis of beta-amino acids using hexahydrobenzoxazolidinones as chiral auxiliaries

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ABSTRACT

A practical synthetic route for the asymmetric synthesis of β^2-amino acids is described. In the first step, the procedure involves the N-acylation of readily available, enantiopure hexahydrobenzoxazolidinone (4*R*,5*R*)-**1** with 3-methylbutanoyl chloride **2**, 4-methylpentanoic acid **3**, and 3-(1-*tert*-butoxycarbonyl)-1*H*-indol-3-yl)propanoic acid **4** to afford derivatives **5a**, **5b**, and **5c**, respectively, which were alkylated with high diastereoselectivity by means of reaction between their sodium enolates and benzyl bromoacetate. Removal of the chiral auxiliary from the alkylated products followed by hydrogenation and hydrolysis gave β^2-amino acids (*S*)-**10a**, (*S*)-**10b**, and (*S*)-**10c**, which were *N*-protected with Fmoc. Enantiomeric (*R*)-**10a–c** were similarly prepared from the isomeric hexahydrobenzoxazolidinone (4*S*,5*S*)-**1**; thus, the route presented here provides access to both enantiomers of valuable highly enantioenriched β^2-amino acids.

1. Introduction

The development of synthetic procedures to obtain β-amino acids is a relevant endeavor since these homologues of α-amino acids play a significant role in medicinal chemistry.[1] Furthermore, β-amino acids have long been employed as precursors for β-lactams, and more recently have gained attention as building blocks for oligomers with well-defined folding behavior, 'foldamers'.[2] Moreover, pioneering works by Seebach et al.[3] and Gellman et al.[4] have demonstrated the folding propensity of oligomers of these compounds, leading to secondary and tertiary structures very similar to those of α-peptides, hence they are considered as excellent peptidomimetics.[5] One can distinguish between the β^2- and β^3-amino acids depending on the position of the side chain in the β-amino acid skeleton.[6]

Proteinogenic α-amino acids are constituents of all enzymes which control the function and metabolism in living organisms, whereas β-amino acids occur mainly as constituents of distinct natural products, such as peptides. The incorporation of β-amino acids instead of their α-analogues increases the stability of peptides against degradation by mammalian peptidases;[3] therefore, β-amino acids are an important tool in the development of drugs capable of withstanding hydrolytic degradation for prolonged periods of time.[7]

For these reasons, numerous methodologies for the synthesis of racemic and enantiomerically pure β-amino acids have emerged.[1] Noticeably, the Arndt–Eistert homologation of α-amino acids allows the preparation of β^3-amino acids bearing functional groups on their side chains in a few steps.[8]

The preparation of β^2-amino acids is much more challenging, and several useful strategies are reported for the synthesis of β^2-amino acids bearing trivial[9] or functionalized[10] side chains.

The use of chiral auxiliaries is another methodology employed for the synthesis of enantiopure α- and β-amino acids. In this context, Juaristi et al.[11] reported a convenient procedure for the preparation of both pairs of enantiomeric hexahydrobenzoxazolidin-2-ones (*R*,*R*)-**1** and (*S*,*S*)-**1** from inexpensive cyclohexene oxide and (*S*)-α-phenylethylamine (Fig. 1). These authors have also described the use of (*R*,*R*)-**1** and (*S*,*S*)-**1** as effective chiral auxiliaries for the stereoselective alkylation, acylation, and aldol condensation of propionic and hydrocinnamic acids.[12] The application of hexahydrobenzoxazolidinones (*R*,*R*)-**1** and (*S*,*S*)-**1** as chiral sulfinyl transfer reagents has recently been reported.[13] In addition, Juaristi et al.[14] described the application of *trans*-hexahydrobenzoxazolidinones (*R*,*R*)-**1** and (*S*,*S*)-**1** in the asymmetric synthesis of aminophosphonic acids AP-3 and AP-4.

Herein we report the use of *trans*-hexahydrobenzoxazolidinones (*R*,*R*)-**1** and (*S*,*S*)-**1** in the enantioselective synthesis of both enantiomers of β^2-homovaline, β^2-homoleucine, and β^2-homotryptophan.

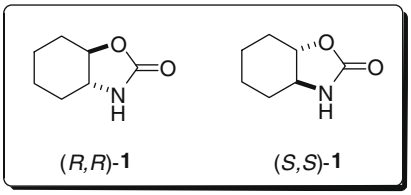

Figure 1. Hexahydrobenzoxazolidinones (*R*,*R*)-**1** and (*S*,*S*)-**1**.

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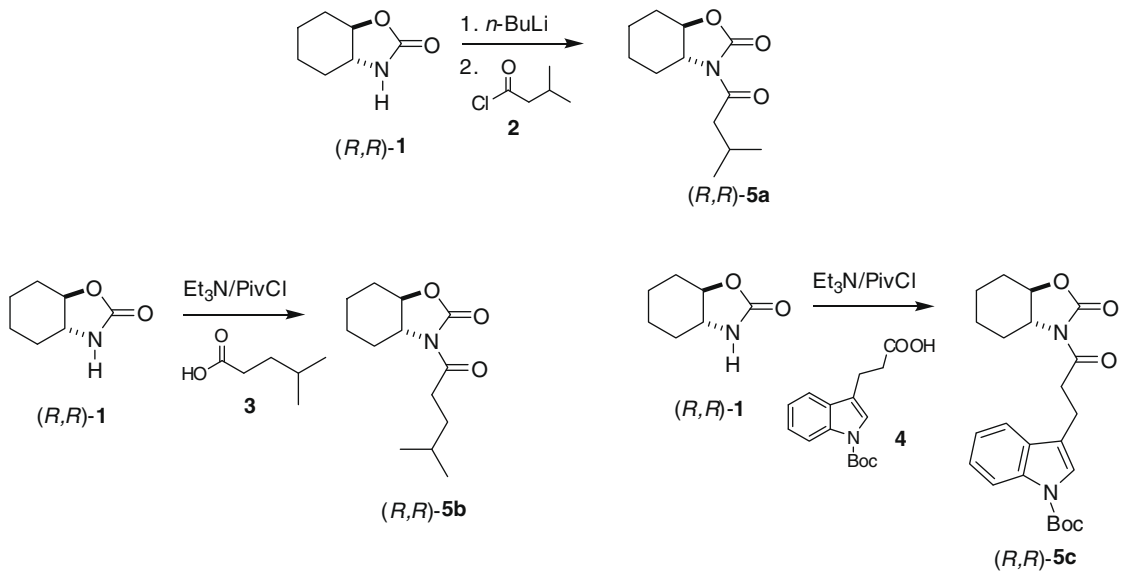


Scheme 1. Synthesis of N-acylated hexahydrobenzoxazolidin-2-ones (*R*,*R*)-**5a–c**. A similar scheme can be applied to reactions carried out with (*S*,*S*)-**1** as the starting material.

2. Results and discussion

2.1. N-Acylation of enantiopure hexahydrobenzoxazolidinone (*R*,*R*)-5

trans-Hexahydrobenzoxazolidinone (*R*,*R*)-**1** was N-acylated following the established protocol,[15] by treatment with *n*-butyllithium at −78 °C, followed by the addition of 3-methylbutanoyl chloride **2** to generate derivative (*R*,*R*)-**5a**. By the same token, derivatives (*R*,*R*)-**5b** and (*R*,*R*)-**5c** were prepared by treatment of (*R*,*R*)-**1** with acid chlorides derived from carboxylic acids **3** and **4**, respectively, in the presence of pivaloyl chloride and triethyl amine at −30 °C (Scheme 1).

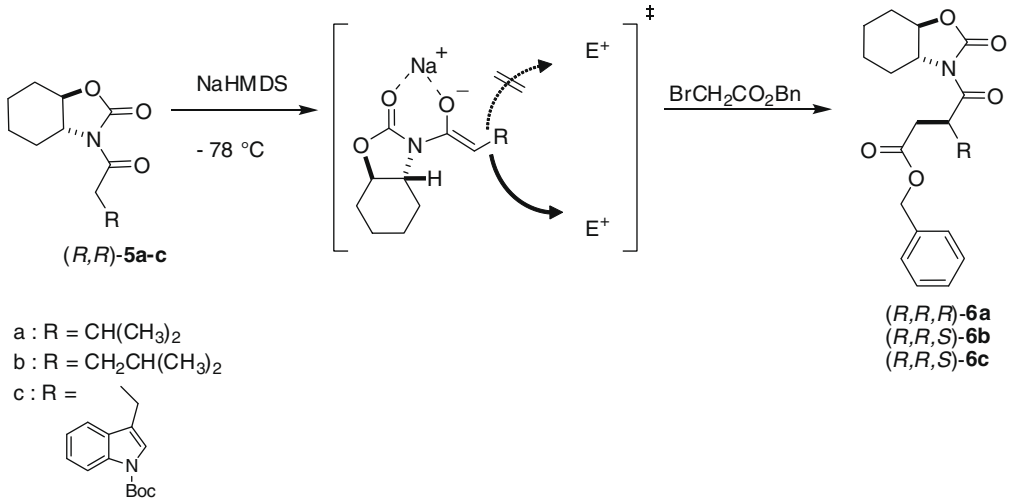
2.2. Diastereoselective alkylation of N-acylated hexahydrobenzoxazolidin-2-ones 5a–c

The sodium enolates derived from (*R*,*R*)-**5a–c** and (*S*,*S*)-**5a–c**, generated with sodium hexamethyldisilazide (NaHMDS), were treated with 2.0 equiv of benzyl bromoacetate at −78 °C for 5 h.[16] Most relevant, ^{1}H NMR analysis of crude alkylated products **6a–c** showed a single set of signals, indicating a diastereomeric purity greater than 98%.

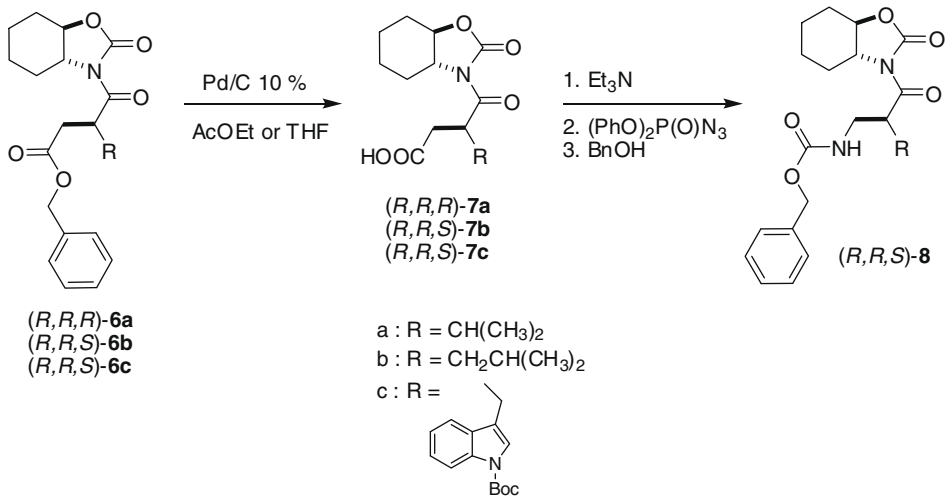
The absolute configuration of the newly created stereogenic center at C(α) in products **6b** and **6c** was established as (*S*), whereas in **6a**, the configuration was assigned as (*R*) owing to a change in priority of the substituents at C(α). This result is consistent with the intermediacy of a (*Z*)-configured enolate,[17] where the sodium cation is chelated by both carbonyl oxygens in the enolate, and the electrophile is incorporated from the less sterically hindered face (Scheme 2).

2.3. Hydrogenolisis of α-alkylated hexahydrobenzoxazolidin-2-ones 6a–c and Curtius rearrangement of the derived carboxylic acids 7a–c

Compounds **6a**, **6b**, and **6c** were hydrogenated with Pd/C 10% at atmospheric pressure to afford carboxylic acid derivatives **7a–c**, which were subjected to Curtius rearrangement by treatment with diphenyl phosphoryl azide, in the presence of Et_3N and benzyl alcohol to give carbamates **8a–c** (Scheme 3).



Scheme 2. Diastereoselective alkylation of N-acylated hexahydrobenzoxazolidin-2-ones (*R*,*R*)-**5a–c**. A similar scheme can be applied to reactions carried out with (*S*,*S*)- **5a–c**.



Scheme 3. Hydrogenolysis and Curtius rearrangement of α-alkylated hexahydrobenzoxazolidin-2-ones (*R,R*)-**6a–c** to give carbamates **8a–c**. A similar scheme can be applied to reactions carried out with (*S,S*)-**6a–c**.

Crystallization of carbamate (*R,R,S*)-**8a** from ethyl acetate–hexane (1:9) afforded suitable crystals for X-ray diffraction structural analysis (Fig. 2).[18]

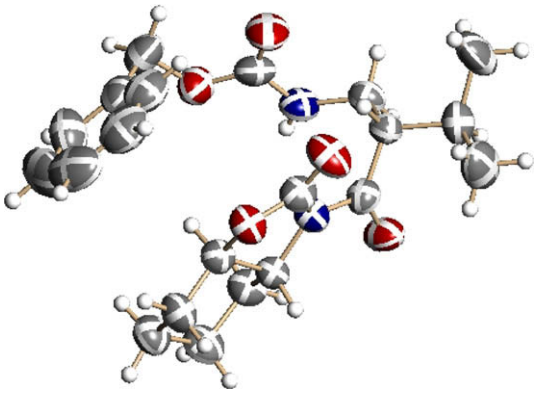


Figure 2. X-ray crystallographic structure and solid state conformation of (*R,R,S*)-**8a**.[18]

Examination of Figure 2 confirms that the alkylation reaction takes place on the less sterically hindered face of the enolates derived from N-acylated substrates **5a–c**, as discussed in Section 2.2.

2.4. Removal of the chiral auxiliary, hydrogenation, and protection with Fmoc

The removal of the oxazolidinone chiral auxiliary from compounds (*S*)-**8a** and (*S*)-**8b** was achieved with lithium hydroperoxide, as suggested by Evans et al.[16,17] These reactions proceed in 53% and 70% yield, respectively, and the resulting products (*S*)-**9a** and (*S*)-**9b** were reduced by catalytic hydrogenation to afford β-amino acids (*S*)-**10a** and (*S*)-**10b** in 89% and 81% yield, respectively. Removal of the chiral auxiliary in compound (*S*)-**9c** was achieved by treatment with *n*-BuLi and BnOH to obtain the benzylated derivative in 47% yield, and the resulting adduct was hydrogenated to give the β-amino acid (*S*)-**10c** in 65% yield. Finally, the protection of β-amino acids (*S*)-**10a–c** was achieved by treatment with Fmoc-Osu, in acetone and sodium carbonate 0.15 M (1:1) to afford the *N*-Fmoc-protected β-amino acids (*S*)-**11a–c** in 45-65% yield (Scheme 4).

2.5. HPLC analysis

HPLC analysis confirmed the efficiency of the present approach for the preparation of enantiomerically pure β^2-homovaline, β^2-homoleucine, and β^2-homotryptophan, which were obtained in 99.4%, 96.0%, and 90% enantiomeric excess, respectively (Fig. 3). Since the alkylation reaction of N-acylated hexahydrobenzoxazolidin-2-ones **5a–c** proceeds with greater than 98% diastereoselectivity, we ascribed the lower enantiomeric excess in two cases to the presence of minor amounts of enantiomeric *trans*-hexahydrobenzoxazolidinone (*S,S*)-**1** in the starting substrate (*R,R*)-**1**, which at the end afforded a small amount of the undesired enantiomeric amino acid.

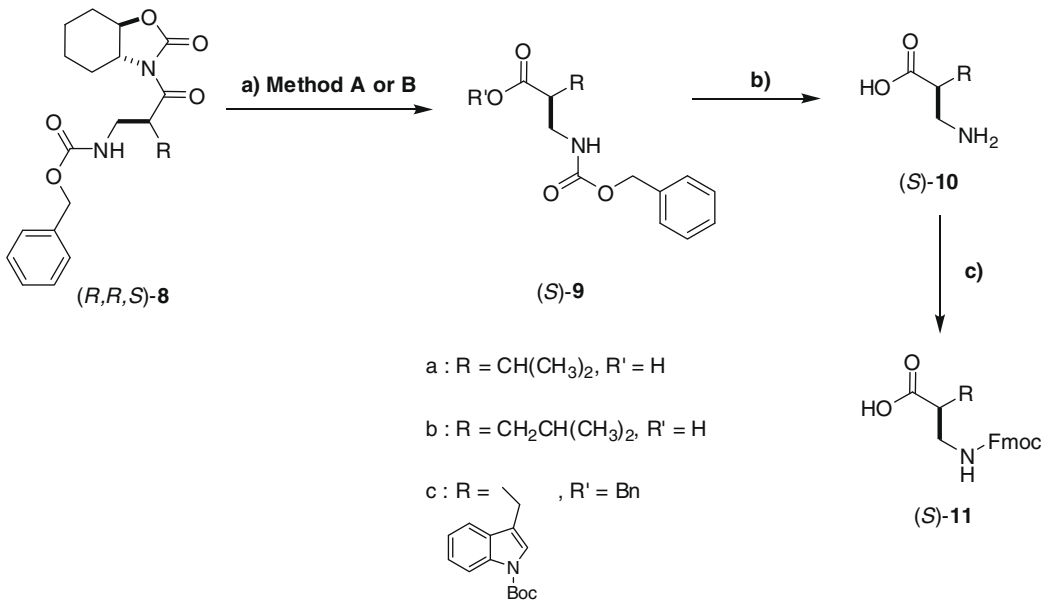
3. Conclusion

An efficient synthetic route that provides both enantiomers of β^2-amino acids from hexahydrobenzoxazolidinones (*R,R*)-**1** and (*S,S*)-**1** was developed. In particular, N-acylated derivatives (*S,S*)-**6** and (*R,R*)-**6**, which were prepared by N-acylation of *trans*-hexahydrobenzoxazolidinones (*S,S*)-**1** and (*R,R*)-**1**, were alkylated with very high diastereoselectivity to afford products which were deprotected, subjected to Curtius rearrangement, and finally converted into the desired enantioenriched β^2-homovaline, β^2-homoleucine, and β^2-homotryptophan.

4. Experimental

4.1. General

Flasks, stirring bars, and hypodermic needles used for the generation and reactions of organometallic compounds were dried for ca. 12 h at 120 °C and allowed to cool in a desiccator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone/ketyl radical. *n*-Butyllithium was titrated according to the method of Juaristi et al.[19] TLC: Merck DC-F254 plates, detection by UV light, iodine vapor, or ninhydrin spray. Flash chromatography: Merck silica gel (0.040–0.063 mm). Melting points: Melt Temp apparatus, not corrected. ^{1}H NMR spectra: Jeol Eclipse-400 (400 MHz), Bruker Ultra Shield (300 MHz), and Jeol GSX-270 (270 MHz) spectrometers; ^{13}C NMR spectra: Jeol Eclipse-400 (100 MHz) and Bruker Ultra Shield (75 MHz); ^{31}P NMR spectra: Jeol Eclipse-400 (162 MHz) and Bruker Ultra Shield



Scheme 4. Reagents and conditions: (a) Method A: LiOH·H_2O, THF–H_2O (1:1), H_2O_2. Method B: (a) BnOH, *n*-BuLi, THF; (b) Pd/C, H_2, EtOH; (c) acetone–Na_2CO_3 0.15 M (1:1), Fmoc-Osu. A similar scheme can be applied to reactions carried out with (*S*,*S*,*R*)- **8a–c**).

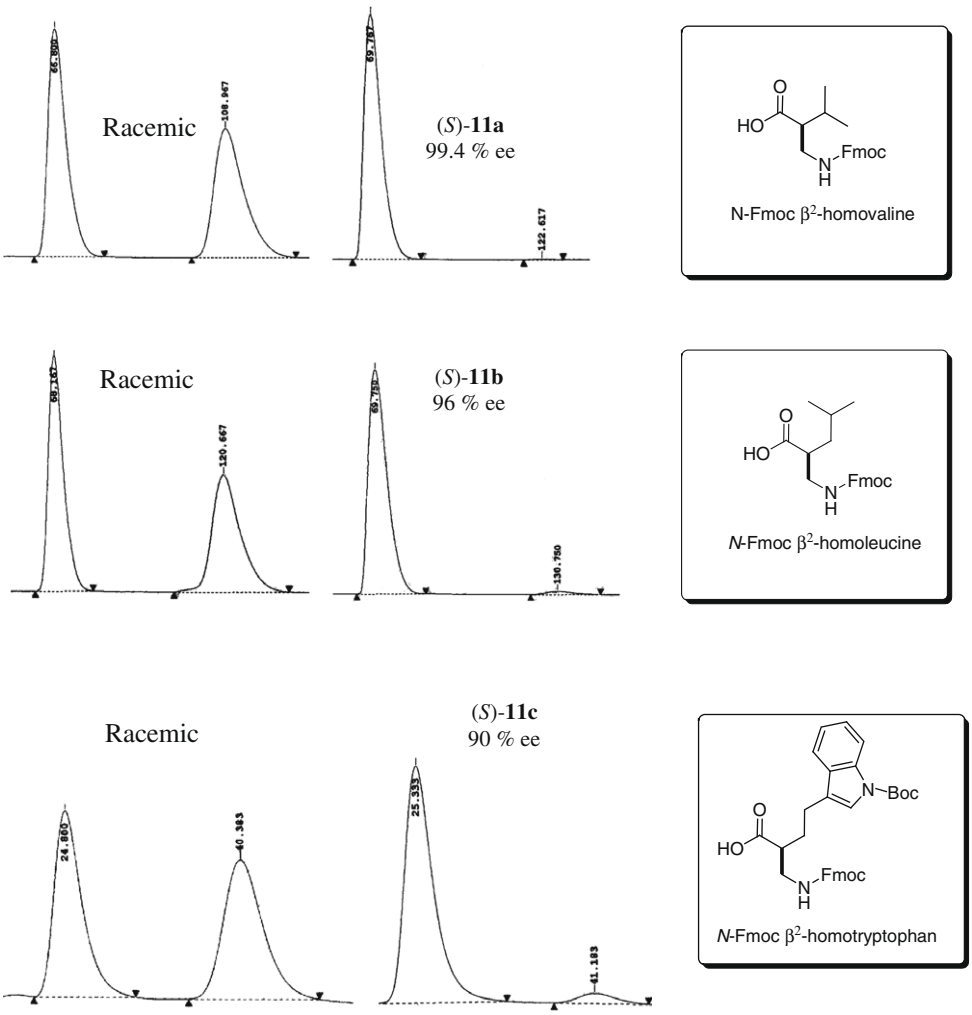


Figure 3. HPLC (*Chiralcel OD*, λ = 210 nm, elution system: *i*-PrOH–hexane–TFA; 10:90:0.1, for (*S*)-**11a** and (*S*)-**11b.** *Chiralcel OD-H*, λ = 210 nm, elution system: *i*-PrOH–hexane–TFA; 20:80:0.1, for (*S*)-**11c**).

(121 MHz) spectrometers. Chemical shifts δ are given in parts per million relative to Me_4Si as an internal reference; coupling constants are given in J (Hertz). Mass spectra were obtained in a Hewlett–Packard HP-5986 instrument. High-resolution mass spectra (HRMS) were obtained on an HPLC 1100 coupled to MSDTOF Agilent Technologies mod. 1969A.

4.2. N-Acylation procedure for the preparation of 5a

n-BuLi (2.35 M, 28.3 mmol, 1 equiv) was added to a cold (−20 °C) solution of hexahydrobenzoxazolidin-2-one (*R*,*R*)- or (*S*,*S*)-**1** (28.3 mmol, 1 equiv) in THF (100 mL) and the resulting mixture was stirred for 30 min at −20 °C. The corresponding acid chloride (28.3 mmol, 1 equiv) was added for 15 min and the reaction mixture was stirred for 12 h at room temperature, before the addition of saturated aqueous NH_4Cl (100 mL), H_2O (80 mL), and EtOAc (150 mL). The organic phase was separated and washed with brine (100 mL), whereas each aqueous fraction was re-extracted with EtOAc (2 × 80 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo.

4.2.1. (4*R*,5*R*)-3-(3-Methylbutanoyl)hexahydrobenzoxazolidin-2-one, (*R*,*R*)-5a

The general procedure described above was followed and the crude product was purified by flash chromatography using ethyl acetate–hexane (80:20) as eluent to give 98% yield of the desired product, mp 89–90 °C. $[\alpha]_D^{25} = -72$ (*c* 1.02, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 2994, 2954, 1798, 1690, 1368, 1332, 1214, 1150. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.94 (d, 3H, J = 3.2), 0.96 (d, 3H, J = 3.2), 1.42 (m, 3H), 1.66 (m, 1H), 1.85 (m, 2H), 2.18 (m, 2H), 2.78 (m, 3H), 3.54 (ddd, 1H, $J_1 \approx J_2$ = 10.6, J_3 = 3.0), 3.86 (ddd, 1H, $J_1 \approx J_2$ = 11.5, J_3 = 3.6). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 22.8(2xC), 23.9, 24.1, 25.6, 28.8, 29.2, 45.4, 63.4, 81.6, 153.1, 175.3; MS (20 eV): *m*/*z* 225 (M^+), 210, 183, 166, 142, 123, 110, 98, 81, 69, 57, 41. Elemental Anal. Calcd for $C_{12}H_{19}O_3N$: C, 63.97; H, 8.50; N, 6.22. Found: C, 64.24; H, 8.39; N, 6.07.

4.2.2. (4*S*,5*S*)-3-(3-Methylbutanoyl)hexahydrobenzoxazolidin-2-one, (*S*,*S*)-5a

The general procedure described above was followed, and the crude product was purified by flash chromatography using ethyl acetate–hexane (80:20) as eluent to give 94% yield of the desired product, mp 90–91 °C. $[\alpha]_D^{25} = +72$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 2954, 2868, 1798, 1690, 1470, 1370, 1332, 1312, 1254, 1214. The ^1H and ^{13}C NMR data were identical to those recorded for enantiomeric (*R*,*R*)-**5a**. MS (20 eV): *m*/*z* 225 (M^+), 210, 183, 166, 142, 123, 110, 98, 81, 69, 57, 41. Elemental Anal. Calcd for $C_{12}H_{19}O_3N$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.62; H, 8.40; N, 6.12.

4.3. N-Acylation procedure for the preparation of 5b and 5c

To a solution of carboxylic acid **3** or **4** (10.4 mmol, 1.05 equiv) in THF (70 mL), were added Et_3N (27 mmol, 2.6 equiv) and pivaloyl chloride (10.8 mmol, 1.05 equiv) at −30 °C. The resulting white suspension was stirred at −30 °C for 90 min, before the addition of LiCl (11.9 mmol, 1.15 equiv) and hexahydrobenzoxazolidin-2-one **1** (10.4 mmol, 1 equiv) in THF (30 mL). The resulting mixture was allowed to warm to room temperature and stirred for 12 h. The mixture was treated with saturated aqueous NH_4Cl (100 mL), H_2O (50 mL), and EtOAc (150 mL). The organic phase was separated, washed with brine (100 mL), and each aqueous fraction was re-extracted with EtOAc (80 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated under vacuum.

4.3.1. (4*R*,5*R*)-3-(4-Methylpentanoyl)hexahydrobenzoxazolidin-2-one, (*R*,*R*)-5b

The crude product was purified by flash chromatography using hexane–ethyl acetate (80:20) to give 92% yield of the desired product, mp 68–69 °C. $[\alpha]_D^{25} = -74$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 2952, 2868, 2372, 1796, 1692, 1472, 1378, 1338, 1310, 1268, 1214, 1148. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.89–3.80 (dt, 1H, J_1 = 3.6 Hz J_2 = 11.4 Hz), 3.56–3.47 (dt, 1H, J_1 = 3.3 Hz J_2 = 10.9 Hz), 2.97–2.74 (m, 3H), 2.23–2.17 (m, 1H), 1.93–1.82 (m, 2H), 1.68– 1.30 (m, 7H), 0.89 (d, 6H, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 176.2, 155.1, 81.6, 63.5, 29.24, 28.81, 28.1, 24.1, 23.9, 22.7 (2 × C). MS (20 eV): *m*/*z* 240 $(M+H)^+$, 196, 183, 152, 142, 110, 98, 81, 71, 55, 43. HR-ESI-TOF Calcd for $C_{13}H_{21}O_3N$ $[M+H]^+$: 240.15942; found: 240.15961.

4.3.2. (4*S*,5*S*)-3-(4-Methylpentanoyl)hexahydrobenzoxazolidin-2-one, (*S*,*S*)-5b

The crude product was purified by flash chromatography using hexane–ethyl acetate (80:20) as eluent to give 98% yield of the desired product, mp 68–69 °C. $[\alpha]_D^{25} = +77$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 2952, 2868, 2362, 1796, 1692, 1472, 1378, 1310, 1268, 1214. The ^1H and ^{13}C NMR data were identical to those recorded for enantiomeric (*R*,*R*)-**5b**. MS (20 eV): *m*/*z* 240 $(M+H)^+$, 196, 183, 152, 142, 110, 98, 81, 71, 55, 43. Elemental Anal. Calcd for $C_{13}H_{21}O_3N$: C, 65.25; H, 8.84; N, 5.85; found: C, 65.48; H, 9.21; N, 5.65.

4.3.3. (4*R*,5*R*)-3-{1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl}-1-oxopropyl-hexahydrobenzoxazolidin-2-one, (*R*,*R*)-5c

Following the procedure described above, the crude product was purified by flash chromatography using hexane–ethyl acetate (80:20) as eluent to give 76% yield of the desired product, mp 127–128 °C. $[\alpha]_D^{25} = -28$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 2942, 2366, 1788, 1724, 1696, 1454, 1390, 1364, 1312, 1156. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.14 (d, 1H, J = 6.8 Hz), 7.6 (d, 1H, J = 7.7 Hz), 7.43 (s, 1H), 7.35–7.23 (m, 2H), 3.95–3.81 (dt, 1H, J_1 = 3.3 Hz, J_2 = 11.4 Hz), 3.61–3.54 (dt, 1H, J_1 = 3.2 Hz J_2 = 10.8 Hz), 3.45–3.34 (m, 1H), 3.27–3.13 (m, 1H), 3.10–2.99 (m, 2H), 2.85–2.82 (m, 1H), 2.25–2.18 (m, 1H), 1.95–1.75 (m, 2H), 1.68 (s, 10H), 1.50–1.25 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 174.7, 154.8, 149.9, 135.6, 130.5, 124.5, 122.9, 122.6, 119.6, 119.1, 115.4, 83.5, 81.6, 63.3, 36.3, 28.9, 28.6, 28.4, 23.8, 23.7, 19.9; MS (20 eV): *m*/*z* 412 (M^+) 412, 356, 312, 171, 130, 57. HR-ESI-TOF Calcd for $C_{23}H_{28}O_5N_2$ [M^++Na]: 435.18904; found: 435.18897.

4.3.4. (4*S*,5*S*)-3-{1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl}-1-oxopropyl-hexahydrobenzoxazolidin-2-one, (*S*,*S*)-5c

Following the procedure described above, the crude product was purified by flash chromatography using hexane–ethyl acetate (80:20) as eluent to give 73% yield of the desired product, mp 123–124 °C. $[\alpha]_D^{25} = +24$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 2936, 1796, 1724, 1694, 1458, 1384, 1352, 1308, 1260, 1210. The ^1H and ^{13}C NMR data were identical to those recorded for enantiomeric (*R*,*R*)-**5c**. MS (20 eV): *m*/*z* 412 (M^+), 412, 356, 312, 171, 130, 57. Elemental Anal. Calcd for $C_{23}H_{28}O_5N_2$: C, 66.97; H, 6.84; N, 6.79. Found: C, 67.05; H, 6.85; N, 6.70.

4.4. General procedure for the alkylation of 5a–c

At first, NaHMDS (1 M solution, 8.98 mmol, 1.1equiv) was added over 15 min to a cold (−78 °C) solution of compound **5** (8.16 mmol, 1 equiv) in THF (80 mL), and the resulting mixture was stirred for an additional 60 min at −78 °C before the slow addition of a solution of benzyl bromoacetate (16.3 mmol, 2 equiv) in THF (20 mL). The reaction mixture was stirred for 5 h at −78 °C, before the addition of saturated aqueous NH_4Cl (100 mL), and the

resulting mixture was warmed to room temperature, diluted with H_2O (50 mL) and EtOAc (2 × 80 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo.

4.4.1. Benzyl-3(*R*)-(isopropyl)-4-[(4*R*,5*R*)-2-oxo-hexahydrobenzoxazolidin-3-yl]-4-oxobuta-noate, (*R,R,R*)-6a

Following the general procedure, the crude product was purified by flash chromatography using hexane–ethyl acetate (90:10) as eluent to give 71% yield of the alkylated product, mp 61–63 °C. $[\alpha]_D^{25} = -5.6$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 2954, 2874, 2358, 1784, 1740, 1688, 1386, 1334, 1186, 1038. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.92 (d, 3H, *J* = 6.9), 1.01 (d, 3H, *J* = 6.8), 1.34 (m, 3H), 1.62 (m, 1H), 1.83 (m, 2H), 2.10 (m, 2H), 2.83 (m, 3H), 3.59 (m, 2H), 3.83 (m, 1H), 5.06 (s, 2H), 7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 18.3, 21.3, 23.9, 24.1, 28.7, 29.0, 29.6, 33.4, 45.7, 63.7, 66.9, 81.7, 128.8, 129.0, 136.2, 154.8, 172.7, 177.2. MS (20 eV): *m*/*z* 373 (M^+), 331, 319, 272, 266, 232, 204, 196, 161, 142, 107, 91, 70, 43. Elemental Anal. Calcd for $C_{21}H_{27}O_5N$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.86; H, 7.00; N, 3.72.

4.4.2. Benzyl-3(*S*)-(isopropyl)-4-[(4*S*,5*S*)-2-oxo-hexahydrobenzoxazolidin-3-yl]-4-oxobutanoate, (*S,S,S*)-6a

Following the general procedure, the crude product was purified by flash chromatography using hexane–ethyl acetate (90:10) as eluent to give 64% yield of the alkylated product, mp 63–64 °C. $[\alpha]_D^{25} = +6.3$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 2956, 2876, 1784, 1738, 1688, 1464, 1386, 1334, 1186. The ^1H and ^{13}C NMR data were identical to those recorded for enantiomeric (*R,R,R*)-**6a**. MS (20 eV): *m*/*z* 373 (M^+), 266, 232, 204, 196, 142, 107, 91, 70. Elemental Anal. Calcd for $C_{21}H_{27}O_5N$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.67; H, 7.90; N, 3.53.

4.4.3. Benzyl-3(*S*)-(isobutyl)-4-[(4*R*,5*R*)-2-oxo-hexahydrobenzoxazolidin-3-yl]-4-oxobutanoate, (*R,R,S*)-6b

Following the general procedure, the crude product was purified by flash chromatography using hexane–ethyl acetate (80:20) as eluent to give 82% yield of the desired alkylated product, mp 60–62 °C. $[\alpha]_D^{25} = +11$ (*c* 1.0, MeOH). IR (KBr, cm^{-1}): ν_{max} 2958, 2362, 1790, 1724, 1688, 1458, 1382, 1312, 1268, 1210. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.39–7.27 (m, 5H), 5.08 (s, 2H), 4.02–3.93 (m, 1H), 3.68–3.60 (dt, 1H, J_1 = 3.5 Hz, J_2 = 11.4 Hz), 3.53–3.45 (dt, 1H, *J* = 3.1 Hz, J_2 = 11.0 Hz), 2.89–2.59 (m, 3H), 2.19–2.15 (m, 1H), 1.94–1.76 (m, 2H), 1.70–1.53 (m, 3H), 1.42–1.13 (m, 4H), 0.94–0.91 (dd, 6H, *J* = 1.8 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 178.0, 172.2, 154.7, 128.8, 128.7, 128.6, 81.7, 66.9, 63.7, 40.4, 39.1, 36.9, 28.7, 25.9, 24.1, 23.8, 21.8. MS (20 eV): *m*/*z* 387 (M^+), 280, 246, 218, 156, 142, 107, 91. HR-ESI-TOF Calcd for $C_{22}H_{29}O_5N$ [M+Na]$^+$: 410.19379; found: 410.19372.

4.4.4. Benzyl-3(*R*)-(Isobutyl)-4-[(4*S*,5*S*)-2-oxo-hexahydrobenzoxazolidin-3-yl]-4-oxobutanoate, (*S,S,R*)-6b

Following the general procedure, the crude product was purified by flash chromatography using hexane–ethyl acetate (80:20) as eluent to give 69% yield of the desired product, mp 63–64 °C. $[\alpha]_D^{25} = -14$ (*c* 1.0, MeOH). IR (KBr, cm^{-1}): ν_{max} 2960, 2370, 1792, 1724, 1688, 1460, 1382, 1312, 1268, 1210. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*R,R,S*)-**6b**. MS (20 eV): *m*/*z* 387 (M^+), 280, 246, 218, 156,142, 107, 91. HR-ESI-TOF Calcd for $C_{22}H_{29}O_5N$ [M+Na]$^+$: 410.19379; found: 410.19392.

4.4.5. Benzyl-3(*S*)-({1-[(*tert*-butoxy)carbonyl]-1*H*-indol-3-yl}-methyl)-4-[(4*R*,5*R*)-2-oxohexa-hydrobenzoxazolidin-3-yl]-4-oxobutanoate, (*R,R,S*)-6c

Following the general procedure, the crude product was purified by flash chromatography using hexane–ethyl acetate (90:10) as eluent to give 83% yield of the desired alkylated product, mp 81–82 °C. $[\alpha]_D^{25} = -31.7$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 2948, 1730, 1692, 1458, 1368, 1258, 1198. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.14 (d, 1H, *J* = 7.0 Hz), 7.89 (d, 1H, *J* = 7.15 Hz), 7.48 (s, 1H), 7.36–7.26 (m, 7H), 5.02 (s, 2H), 4.28–4.21 (m, 1H), 3.78–3.67 (dt, 1H, J_1 = 3.6 Hz, J_2 = 11.3 Hz), 3.61–3.54 (dt, 1H J_1 = 3.0 Hz, J_2 = 11.3 Hz), 3.40–3.34 (dd, 1H, *J* = 3.7 Hz), 2.99–2.89 (dd, 1H, *J* = 10.9 Hz), 2.77–2.48 (m, 4H), 2.22 (d, 1H, *J* = 10.6), 1.94–1.24 (m, 14H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 177.3, 172.1, 154.9, 150.0, 136.0, 130.6, 129.0, 128.8, 128.7, 124.9, 124.8, 123.1, 120.2, 117.3, 115.5, 83.9, 83.4, 66.7, 63.8, 41.0, 36.5, 28.8, 28.6, 27.1, 24.0, 23.9. MS (20 eV): *m*/*z* 560 (M^+), 460, 369, 311, 200, 130, 91, 41. HR-ESI-TOF Calcd for $C_{32}H_{36}O_7N_2$ [M+Na]$^+$: 583.24147; found: 583.24189.

4.4.6. Benzyl-3(*R*)-({1-[(*tert*-butoxy)carbonyl]-1*H*-indol-3-yl}-methyl)-4-[(4*S*,5*S*)-2-oxohexa-hydrobenzoxazolidin-3-yl]-4-oxobutanoate, (*S,S,R*)-6c

Following the general procedure, the crude product was purified by flash chromatography using hexane–ethyl acetate (90:10) as eluent to give 63% yield of the desired alkylated product, mp 83–84 °C. $[\alpha]_D^{25} = +34$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 2948, 1798, 1730, 1692, 1458, 1368, 1258, 1198. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*R,R,S*)-**6c**. MS (20 eV): *m*/*z* 560 (M^+), 460, 369, 311, 228, 200, 130, 91, 41. Elemental Anal. Calcd for $C_{32}H_{36}O_7N_2$: C, 68.55; H, 6.47; N, 5.00. Found: C, 68.65; H, 6.75; N, 4.98.

4.5. General procedures for the hydrogenolysis of alkylated products 6

4.5.1. Method A

A solution of compound **6** (12 mmol) in EtOAc (100 mL) was stirred under H_2 (1 atm) in the presence of 10% of Pd/C for 12 h. The catalyst Pd/C was filtered off, washed with EtOAc, and the filtrate was concentrated in vacuo.

4.5.1.1. 3(*R*)-(Isopropyl)-4-[(4*R*,5*R*)-2-oxo-hexahydrobenzoxazolidin-3-yl]-4-oxobutanoic acid, (*R,R,R*)-7a. The crude product was purified by flash chromatography using ethyl acetate–hexane (1:1) as eluent to give the desired product as a yellow oil in 98% yield. $[\alpha]_D^{25} = -25.4$ (*c* 1.0, $CHCl_3$); IR (KBr, cm^{-1}): ν_{max} 2958, 1788, 1696, 1466, 1370, 1308, 1252, 1204, 1144, 1116. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.87 (d, 3H, *J* = 8.8), 0.99 (d, 3H, *J* = 6.8), 1.41 (m, 3H), 1.63 (m, 1H), 1.85 (m, 2H), 2.09 (m, 1H), 2.22 (m, 1H), 2.54 (dd, 1H, *J* = 17.4), 2.84 (dd, 2H, *J* = 17.4), 3.56 (ddd, 1H, $J_1 \approx J_2$ = 11.0, J_3 = 3.4), 3.74 (m, 1H), 3.89 (ddd, 1H, $J_1 \approx J_2$ = 11.7, J_3 = 3.6). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ (ppm): 17.9, 20.9, 23.6, 23.9, 28.5, 28.8, 29.1, 32.7, 45.2, 63.6, 81.8, 154.6, 176.8, 178.8. MS (20 eV): *m*/*z* 283 (M^+), 241, 224, 206, 179, 142, 124, 112, 98, 70, 55, 43. HR-ESI-TOF Calcd for $C_{14}H_{21}O_5N$ [M+Na]$^+$: 306.1311, found: 306.1303.

4.5.1.2. 3(*S*)-(Isopropyl)-4-[(4*S*,5*S*)-2-oxo-hexahydrobenzoxazolidin-3-yl]-4-oxobutanoic acid, (*S,S,S*)-7a. The crude product was purified by flash chromatography using ethyl acetate–hexane (1:1) as eluent to give the desired product as a yellow oil in 93% yield. $[\alpha]_D^{25} = +25.5$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 2956, 1790, 1704, 1468, 1360, 1306, 1252, 1204, 1144, 1116. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*R,R,R*)-**7a**. MS (20 eV): *m*/*z* 283 (M^+), 241, 224, 206, 179, 142, 124, 112, 98, 70, 55, 43. HR-ESI-TOF calcd for $C_{14}H_{21}O_5N$ [M+Na]$^+$: 306.1311; found: 306.1303.

4.5.1.3. 3(*S*)-(Isobutyl)-4-[(4*R*,5*R*)-2-oxo-hexahydrobenzoxazolidin-3-yl]-4-oxobutanoic acid, (*R,R,S*)-7b. The crude product was purified by flash chromatography using hexane–ethyl acetate

(1:1) as eluent to give 95% yield of the desired hydrogenolyzed product, mp 98–100 °C. $[\alpha]_D^{25} = +6$ (*c* 1, MeOH). IR (KBr, cm^{-1}): ν_{max} 3308, 2954, 2876, 2362, 1790, 1738, 1676, 1400, 1350. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 11.3 (br s, 1H), 3.92–3.84 (m, 2H), 3.58–3.51 (dt, 1H, J_1 = 2.9 Hz, J_2 = 10.4), 2.81–2.55 (m, 3H), 2.23–2.16 (m, 1H), 1.93–1.82 (m, 2H), 1.69-1.62 (m, 3H), 1.45–1.20 (m, 4H), 0.91 (d, 6H, *J* = 5.8 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 178.5, 177.7, 154.5, 81.8, 63.5, 39.9, 38.6, 36.2, 28.6, 28.5, 25.7, 23.8, 23.6, 21.4. MS (20 eV): *m*/*z* 297 (M^+), 254, 241, 192, 142, 98, 69, 56, 43. HR-ESI-TOF Calcd for $C_{15}H_{23}O_5N$ $[M+Na]^+$: 298.16490, found: 298.16461.

4.5.1.4. 3(*R*)-(Isobutyl)-4-[(4*S*,5*S*)-2-oxo-hexahydrobenzoxazolidin-3-yl]-4-oxobutanoic acid, (*S*,*S*,*R*)-7b. The crude product was purified by flash chromatography using hexane–ethyl acetate (1:1) as eluent to give 93% yield of the desired hydrogenolyzed product, mp 98–99 °C. $[\alpha]_D^{25} = -8$ (*c* 1, MeOH). IR (KBr, cm^{-1}): ν_{max} 3306, 2954, 2876, 2362, 1790, 1738, 1676, 1400, 1312. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*R*,*R*,*S*)-**7b**. MS (20 eV): *m*/*z* 297 (M^++1), 254, 241, 192, 142, 98, 69, 56, 43. Elemental Anal. Calcd for $C_{15}H_{23}O_5N$: C, 60.59; H, 7.80; N, 4.71. Found: C, 60.28; H, 7.99; N, 4.65.

4.5.2. Method B

A solution of compound **6** (4.20 mmol) in THF (50 mL) was stirred under H_2 (1 atm) in the presence of 10% Pd/C for 2 h. The catalyst Pd/C was filtered off, washed with THF, and the filtrate was concentrated in vacuo.

4.5.2.1. 3(*S*)-({1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl}methyl)-4-[(4*R*,5*R*)-2-oxo-hexahydrobenzoxazolidin-3-yl]-4-oxobutanoic acid, (*R*,*R*,*S*)-7c. Following the described procedure, the residue was purified by crystallization from dichloromethane–hexane (1:20) to give the desired hydrogenolyzed product in 95% yield, mp 80–82 °C. $[\alpha]_D^{25} = -49$ (*c* 1, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 3450, 2942, 1786, 1730, 1456, 1256, 1156. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.12 (d, 1H, *J* = 7.3 Hz), 7.86 (d, 1H, *J* = 7.4 Hz), 7.47 (s, 1H), 7.34–7.24 (m, 2H), 4.19–4.07 (m, 1H), 4.00–3.87 (dt, 1H, J_1 = 32 Hz, J_2 = 11.4 Hz), 3.65–3.61 (m, 1H), 3.40–3.34 (dd, 1H, J_1 = 3.8 Hz, J_2 = 13.9 Hz), 2.94–2.77 (m, 2H), 2.67–2.59 (dd, 1H, J_1 = 10.9 Hz, J_2 = 13.8 Hz), 2.51–2.44 (dd, 1H, J_1 = 3.5 Hz, J_2 = 17.5 Hz), 2.29–2.18 (m, 1H), 1.19–1.84 (m, 2H), 1.68 (s, 10H), 1.44–1.35 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 177.9, 176.9, 154.7, 149.8, 135.7, 130.4, 124.7, 124.6, 122.9, 119.9, 116.9, 115.3, 83.8, 82.1, 63.6, 40.7, 35.9, 28.5 (2 × C), 28.4 (2 × C), 26.7, 23.8, 23.7. MS (20 eV): *m*/*z* 470 (M^+), 370, 273, 229, 130, 57, 41. HR-ESI-TOF Calcd for $C_{25}H_{30}O_7N_2$ $[M+Na]^+$: 493.19452, found: 493.19495.

4.5.2.2. 3(*R*)-({1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl}methyl)-4-[(4*S*,5*S*)-2-oxohexahydrobenzoxazolidin-3-yl]-4-oxobutanoic acid, (*S*,*S*,*R*)-7c. The residue was purified by crystallization using dichloromethane–hexane (1:20) as eluent to give 95% yield of the desired product, mp 82–83 °C. $[\alpha]_D^{25} = +33$ (*c* 1, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 3450, 2948, 1786, 1730, 1454, 1256, 1158. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*R*,*R*,*S*)-**7c**. MS (20 eV): *m*/*z* 470 (M^+), 370, 273, 229, 130, 57, 41. HR-ESI-TOF Calcd for $C_{25}H_{30}O_7N_2$ $[M+Na]^+$: 493.19452, found: 493.19394.

4.6. General procedure for the preparation of compounds 8a–c via Curtius rearrangement of 7a–c

To a stirred solution of compound **7** (7.1 mmol, 1 equiv) in toluene (50 mL) and Et_3N (14.2 mmol, 2 equiv), were added diphenylphosphoryl azide [$(PhO)_2P(O)N_3$, 8.53 mmol, 1.2 equiv)] and BnOH (14.2 mmol, 2 equiv). The resulting mixture was stirred for 1 h at room temperature and then heated at reflux for an additional 2 h. The toluene solvent was evaporated in vacuo and the residue was dissolved in EtOAc (150 mL) and 2 M HCl (70 mL). The organic phase was separated, washed with saturated solution $NaHCO_3$, dried over anhydrous Na_2SO_4, and concentrated in vacuo.

4.6.1. (4*R*,5*R*)-3-[2(*S*)-({[(Benzyloxy)carbonyl]amino}methyl)-3-methyl-butanoyl] hexahydrobenzoxazolidin-2-one, (*R*,*R*,*S*)-8a

The crude product was purified by flash chromatography using dichloromethane–ethyl acetate (90:10) as solvent to give the desired product in 70% yield, mp 72–73 °C. $[\alpha]_D^{25} = -8$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 3356, 2962, 2870, 1764, 1700, 1528, 1260. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 0.97 (d, 3H, *J* = 3.1), 0.98 (d, 3H, *J* = 3.3), 1.35 (m, 3H), 1.59 (m, 1H), 1.78 (m, 1H), 1.88 (m, 1H), 2.07 (m, 1H), 2.17 (m, 1H), 2.75 (d, 1H, *J* = 10.8), 3.48 (m, 3H), 3.72 (m, 2H), 4.96 (s, 1H), 5.08 (dd, 2H, J_1 = 19.4 Hz, J_2 = 12.2 Hz), 7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ (ppm): 19.1, 21.2, 23.5, 23.8, 28.4, 28.8, 41.0, 50.2, 63.3, 66.7, 81.2, 128.3, 128.6, 163.7, 154.5, 156.3, 177.2. MS (20 eV): *m*/*z* 388 (M), 297, 281, 247, 210, 166, 142, 112, 91, 70; Elemental Anal. Calcd for $C_{21}H_{27}O_5N$: C, 64.93; H, 7.27; N, 7.21; found: C, 65.25; H, 7.27; N, 7.00.

4.6.2. (4*S*,5*S*)-3-[2(*R*)-({[(Benzyloxy)carbonyl]amino}methyl)-3-methylbutanoyl] hexahydrobenzoxazolidin-2-one, (*S*,*S*,*R*)-8a

The crude product was purified by flash chromatography using dichloromethane–ethyl acetate (90:10) as eluent to give the desired product in 61% yield, mp 72–73 °C. $[\alpha]_D^{25} = +9$ (*c* 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 3356, 2962, 2870, 1764, 1708, 1528, 1260. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*R*,*R*,*S*)-**8a**. MS (20 eV): *m*/*z* 388 (M^+), 297, 281, 247, 210, 166, 142, 112, 91, 70. Elemental Anal. Calcd for $C_{21}H_{27}O_5N$: C, 64.93; H, 7.27; N, 7.21. Found: C, 65.23; H, 7.57; N, 7.16.

4.6.3. (4*R*,5*R*)-3-[2(*S*)-({[(Benzyloxy)carbonyl]amino}methyl)-4-methyl-pentanoyl] hexahydrobenzoxazolidin-2-one, (*R*,*R*,*S*)-8b

The crude product was purified by flash chromatography using dichloromethane–ethyl acetate (90:10) as eluent to give the desired product in 64% yield, mp 72–73 °C. $[\alpha]_D^{25} = +24$ (*c* 1.0, MeOH). IR (KBr, cm^{-1}): ν_{max} 3338, 2938, 2872, 2374, 1796, 1720, 1686, 1530, 1232, 1144, 1036. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.34–7.27 (m, 5H), 5.08 (s, 2H), 4.03–3.95 (m, 1H), 3.76–3.67 (dt, 1H, J_1 = 3.4 Hz, J_2 = 11.4 Hz), 3.56–3.31 (m, 3H), 2.70–2.65 (m, 1H), 2.19–2.18 (m, 1H), 1.89–1.53 (m, 5H), 1.38–1.19 (m, 4H), 0.91 (t, 6H, *J* = 5.7 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 177.1, 156.3, 154.6, 136.7, 128.6, 128.2, 81.3, 66.7, 63.4, 43.4, 42.6, 37.6, 28.5, 25.8, 23.8, 23.5, 22.9, 22.5. MS (20 eV): *m*/*z* 402 (M^+), 346, 295, 261, 208, 196, 126, 107, 91. HR-ESI-TOF Calcd for $C_{22}H_{30}O_5N_2$ $[M+Na]^+$: 425.20469; found: 425.20488.

4.6.4. (4*S*,5*S*)-3-[2(*R*)-({[(Benzyloxy)carbonyl]amino}methyl)-4-methyl-pentanoyl] hexahydrobenzoxazolidin-2-one, (*S*,*S*,*R*)-8b

The crude product was purified by flash chromatography using dichloromethane–ethyl acetate (90:10) as eluent to give the desired product in 82% yield, mp 74–75 °C. $[\alpha]_D^{25} = -28$ (*c* 1.0, MeOH). IR (KBr, cm^{-1}): ν_{max} 3338, 2936, 2872, 2364, 1796, 1720, 1684, 1530, 1232, 1144, 1036. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*R*,*R*,*S*)-**8b**. MS (20 eV): *m*/*z* 402 (M^+), 346, 295, 261, 208, 196, 126, 107, 91. HR-ESI-TOF calcd for $C_{22}H_{30}O_5N_2$ $[M+Na]^+$: 425.20469; found: 425.20518.

4.6.5. (4*R*,5*R*)-3-[2(*S*)-({[(Benzyloxy)carbonyl]amino}methyl)-3-({1-[(*tert*-butoxy)carbonyl]-1*H*-indol-3-yl}-1-oxo-propyl)-hexahydrobenzoxazolidin-2-one, (*R*,*R*,*S*)-8c

The crude product was purified by flash chromatography using hexane–ethyl acetate (80:20) as eluent to give the desired product in 88% yield, mp 99-100 °C. $[\alpha]_D^{25} = +7.4$ (*c* 1.01, Acetone). IR (KBr,

cm^{-1}): ν_{max} 3410, 3346, 2944, 2366, 1790, 1732, 1456, 1368. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.12 (d, 1H, J = 7.3 Hz), 7.65 (d, 1H, J = 7.4 Hz), 7.35–7.19 (m, 7H), 5.07 (s, 2H), 4.38–4.29 (m, 1H), 3.80–3.71 (dt, 1H, J_1 = 11.4, J_2 = 3.3), 3.58–3.41 (m, 3H), 3.22 (dd, 1H, J_1 = 14.7, J_2 = 5.9 Hz), 2.86–2.71 (m, 2H), 2.18 (m, 2H), 1.91–1.50 (m, 12H), 1.43–1.14 (m, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 175.9, 156.4, 154.7, 149.8, 136.7, 135.6, 128.7, 128.2, 124.6, 124.1, 122.8, 119.3, 117.2, 116.9, 115.3, 83.7, 81.6, 66.8, 63.5, 44.3, 42.6, 28.6, 28.5 (2 × C), 28.3, 24.3, 23.7. MS (20 eV): m/z 575 (M^+) 475, 367, 324, 170, 130, 41. HR-ESI-TOF Calcd for $C_{32}H_{37}O_7N_3$ $[M+Na]^+$: 598.25237; found: 598.25346.

4.6.6. (4*S*,5*S*)-3-[2(*R*)-({[(Benzyloxy)carbonyl]amino}methyl)-3-({1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-3-yl}-1oxo-propyl)-hexahydrobenzoxazolidin-2-one, (*S*,*S*,*R*)-8c

The crude product was purified by flash chromatography using hexane–ethyl acetate (80:20) as eluent to give the desired product in 60% yield, mp 100–101 °C. $[\alpha]_D^{25} = -5.5$ (c 1.0, acetone); IR (KBr, cm^{-1}): ν_{max} 3410, 3346, 2944, 2362, 1792, 1730, 1522, 1458, 1372. The ^{1}H and ^{13}C NMR data were identical to those recorded in enantiomeric (*R,R,S*)-**8c**. MS (20 eV): m/z 575 (M^+), 475, 367, 324, 170, 130, 41. Elemental Anal. Calcd for $C_{32}H_{37}O_7N_3$: C, 66.77; H, 6.48; N, 7.30. Found: C, 67.10; H, 6.31; N, 7.27.

4.7. General procedures for the preparation of derivatives 9

4.7.1. Method A

The reaction was carried out in two steps:

Flask A: To a stirred solution of $LiOH{\cdot}H_2O$ (1.5 mmol, 2 equiv) in 8 mL of a mixture of THF–H_2O (1:1) was added H_2O_2 (30% aq solution; 2.98 mmol, 4 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for 3 min.

Flask B: A stirred solution of compound **8** (0.75 mmol, 1 equiv) in THF (8 mL) was cooled to 0 °C before the solution previously prepared in flask A was added via cannula. The reaction mixture was stirred at 0 °C for 30 min before the addition of $NaSO_3$ (2.68 mmol, 4 equiv) in H_2O (4 mL). The mixture was stirred a 0 °C for 30 additional minutes, treated with H_2O (10 mL), and extracted with EtOAc (2 × 20 mL). The aqueous phase was acidified to pH 2 with 1 M HCl at 0 °C. A white solid precipitated, which was extracted with EtOAc (3 × 25 mL), the organic phase was separated, washed with a saturated solution of sodium and potassium tartrate, and dried over anhydrous Na_2SO_4 and concentrated in vacuo.

4.7.1.1. 2(*S*)-([{(Benzyloxy)carbonyl}amino]methyl)-3-methyl-butanoic acid, (*S*)-9a. The general procedure (Method A) was followed and the crude product was purified by flash chromatography using dichloromethane–methanol (90:10) as eluent to give the desired product as a colorless oil in 53% yield. $[\alpha]_D^{25} = +18$ (c 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 3332, 3034, 2964, 1728, 1724, 1720, 1586, 1266. ^{1}H NMR (DMSO-d_6, 270 MHz, 120 °C) δ (ppm): 0.93 (d, 3H, J = 6.9), 0.96 (d, 3H, J = 6.9), 1.89 (ddd, 1H, $J_1 \approx J_2$ = 13.3, J_3 = 6.7), 2.35 (m, 1H), 3.24 (m, 2H), 5.04 (s, 2H), 6.62 (s, 1H), 7.33 (m, 5H). ^{13}C NMR (DMSO-d_6, 67.9 MHz, 120 °C) δ (ppm): 179.8, 158.1, 136.3, 128.5, 128.1, 127.8, 67.4, 52.4, 40.5, 28.7, 20.2 (2 × C). MS (20 eV): m/z 265 (M^+), 250, 247, 173, 141, 108, 91, 70. HR-ESI-TOF: Calcd for $C_{14}H_{19}O_4N$ $[M+Na]^+$: 288.12063; found: 288.12027.

4.7.1.2. 2(*R*)-([{(Benzyloxy)carbonyl}amino]methyl)-3-methyl-butanoic acid, (*R*)-9a. The general procedure (Method A) was followed and the crude product was purified by flash chromatography using dichloromethane–methanol (90:10) as eluent to give 36% yield of the desired product as a colorless oil. $[\alpha]_D^{25} = -18.8$ (c 1.0, $CHCl_3$). IR (KBr, cm^{-1}): ν_{max} 3332, 3034, 2964, 1724, 1720, 1526, 1266. The ^{1}H and ^{13}C NMR data were identical to those recorded in enantiomeric (*S*)-**9a**. MS (20 eV): m/z 265 (M^+), 250, 247, 173, 141, 108, 91, 70. HR-ESI-TOF: Calcd for $C_{14}H_{19}O_4N$ $[M+Na]^+$: 288.12063; found: 288.12089.

4.7.1.3. 2(*S*)-([{(Benzyloxy)carbonyl}amino]methyl)-4-methyl-pentanoic acid, (*S*)-9b. The general procedure (Method A) was followed and the crude product was purified by flash chromatography using dichloromethane–methanol (90:10) as eluent to give 70% yield of the desired product, mp 74–76 °C. $[\alpha]_D^{25} = +12.5$ (c 1.0, MeOH). IR (KBr, cm^{-1}): ν_{max} 3348, 3186, 2956, 2360, 1718, 1536, 1462. ^{1}H NMR (DMSO-d_6, 300 MHz, 100 °C) δ (ppm): 7.61–7.28 (m, 5H), 6.8 (br s, 1H), 5.04 (s, 2H), 3.29–3.10 (m, 2H), 2.60–2.49 (m, 1H), 1.66-1.23 (m, 3H), 0.87 (d, 6H, J = 6.5 Hz). ^{13}C NMR (DMSO-d_6, 75.5 MHz, 100 °C) δ (ppm): 176.3, 156.9, 138.2, 129.1, 128.4, 128.3, 66.2, 44.6, 39.5, 26.5, 23.5, 22.8. MS (20 eV): m/z 279 (M^+), 261, 223, 115, 108, 91, 79, 57, 43. HR-ESI-TOF: Calcd for $C_{15}H_{21}O_4N$ $[M+H]^+$: 280.15433; found: 280.15414.

4.7.1.4. 2(*R*)-([{(Benzyloxy)carbonyl}amino]methyl)-4-methyl-pentanoic acid, (*R*)-9b. The general procedure (Method A) was followed and the crude product was purified by flash chromatography using dichloromethane–methanol (90:10) as eluent to give the desired product in 63% yield, mp 88–89 °C. $[\alpha]_D^{25} = -11$ (c 1.0, MeOH). IR (KBr, cm^{-1}): ν_{max} 3310, 3178, 2956, 2366, 1720, 1550, 1462. The ^{1}H and ^{13}C NMR data were identical to those recorded in enantiomeric (*S*)-**9b**. MS (20 eV): m/z 279 (M^+), 261, 223, 115, 108, 91, 79, 57, 43. HR-ESI-TOF: Calcd for $C_{15}H_{21}O_4N$ $[M+H]^+$: 280.15433; found: 280.15473.

4.7.2. Method B

The reaction was carried out in two steps:

Flask A: To a stirred solution of benzyl alcohol (4.1 mmol, 2.36 equiv) in THF (7 mL) at −78 °C was added *n*-BuLi (2.21 M in hexane, 2.71 mmol, 1.56 equiv) and the resulting mixture was stirred for 5 min.

Flask B: The solution mixture prepared in flask A was added at −78 °C to a stirred solution of compound **8** (1.74 mmol, 1 equiv) in THF (20 mL). The reaction mixture was stirred for 15 min at −78 °C and then the temperature was allowed to rise to 0 °C. Stirring was continued for 2 h before saturated aqueous NH_4Cl (20 mL) was added, and the mixture was diluted with H_2O (5 mL) and EtOAc (60 mL). The organic phase was separated and washed with brine solution, which was re-extracted with EtOAc (2 × 30 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and concentrated in vacuo.

4.7.2.1. Benzyl-2(*S*)-({[(Benzyloxy)carbonyl]amino}methyl)-3-{1-[(*tert*-butoxy)carbonyl]-1*H*-indol-3yl}-propanoate, (*S*)-9c. The general procedure (Method B) was followed and the crude product was purified by flash chromatography using hexane–ethyl acetate (60:40) as eluent to give the desired product as an oil in 47% yield. $[\alpha]_D^{25} = +6.5$ (c 1.85, MeOH). IR (KBr, cm^{-1}): ν_{max} 3362, 2930, 2360, 1732, 1518, 1454, 1370, 1160. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.15 (bs, 1H), 7.51–7.18 (m, 14H), 5.09 (d, 2H, J = 2.2 Hz), 5.04 (s, 2H), 3.60–3.41 (m, 2H), 3.18–3.06 (m, 2H), 2.98–2.90 (m, 1H), 1.66 (s, 9H). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ (ppm): 174.18, 156.5, 149.7, 136.5, 135.6, 130.3, 128.6, 128.4, 128.3, 128.2, 128.1, 124.6, 123.8, 122.6, 118.9, 116.9, 115.4, 83.6, 66.9, 66.8, 45.8, 42.3, 28.3, 25.3. MS (20 eV): m/z 542 (M^+), 442, 378, 334, 290, 243, 200, 130, 91, 57. HR-ESI-TOF: Calcd for $C_{32}H_{34}O_6N_2$ $[M+H]^+$: 543.24896; found: 543.24867.

4.7.2.2. Benzyl-2(*R*)-({[(benzyloxy)carbonyl]amino}methyl)-3-{1-[(*tert*-butoxy)carbonyl]-1*H*-indol-3yl}-propanoate, (*R*)-9c. The general procedure (Method B) was followed and the crude product

was purified by flash chromatography using hexane–ethyl acetate (60:40) as eluent to give the desired product as an oil in 31% yield. $[\alpha]_D^{25} = -8.65$ (*c* 1.85, MeOH). IR (KBr, cm^{-1}): ν_{max} 3368, 3032, 2976, 2936, 1728, 1520, 1452, 1372, 1254. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*S*)-**9c**. EM (20 eV): *m*/*z* 542 (M^+), 442, 378, 334, 290, 243, 200, 130, 91, 57. HRMS (FAB): Calcd for $C_{32}H_{34}O_6N_2$ (M^+): 542.2410; found: 542.2417.

4.8. General procedure for the preparation of β-amino acids 10a–c

The corresponding substrate **9** (4.26 mmol,1 equiv) was dissolved in EtOH (75 mL) and stirred with 10% Pd/C under an H_2 atmosphere (1 atm) at room temperature for 4 h. The catalyst Pd/C was filtered off, washed with EtOH, and the filtrate was concentrated in vacuo.

4.8.1. 2(*S*)-([Amino]methyl)-3-methylbutanoic acid, (*S*)-10a

The general procedure was followed and the crude product was purified by flash chromatography using isopropyl alcohol–methanol–ammonium hydroxide (5:2:1) as eluent to give the desired product in 89% yield, mp 228–230 °C. $[\alpha]_D^{25} = +13$ (*c* 1.0, H_2O) for 98% ee, Chirobiotic T, MeOH–H_2O (80:20), 1 mL/min, 205 nm, *t* = 8.18 min; [Lit.[20] mp 228–230 °C. $[\alpha]_D^{25} = -11.4$ (*c* 1.0, H_2O), (*R*)]. IR (KBr, cm^{-1}): ν_{max} 2968, 2664, 2204, 1550, 1408. NMR ^1H (D_2O, 270 MHz) δ (ppm): 0.89 (d, 3H, *J* = 6.7), 0.93 (d, 3H, *J* = 6.9), 1.94 (ddd, 1H, $J_1 \approx J_2 = 13.5$, $J_3 = 6.9$), 2.3 (m, 1H), 3.09 (m, 2H); NMR ^{13}C (D_2O, 67.9 MHz) δ (ppm): 18.7, 20.0, 28.6, 39.0, 52.0, 180.5. EM (20 eV): *m*/*z* 131 (M^+), 89, 83, 70, 55, 44; HR-ESI-TOF: Calcd for $C_6H_{13}O_2N$ $[M+H]^+$: 132.10191, found: 132.10228.

4.8.2. 2(*R*)-([Amino]methyl)-3-methylbutanoic acid, (*R*)-10a

The general procedure was followed and the crude product was purified by flash chromatography using isopropyl alcohol–methanol–ammonium hydroxide (5:2:1) as eluent to give the desired product in 70% yield, mp 238–240 °C. $[\alpha]_D^{25} = -11.4$ (*c* 1.0, H_2O) for 100% ee, Chirobiotic T, MeOH–H_2O (80:20), 1 mL/min., 205 nm, *t* = 7.27 min, [Lit.[20] mp 228–230 °C. $[\alpha]_D^{25} = -11.4$ (*c* 1.0, H_2O)]. IR (KBr, cm^{-1}): ν_{max} 2968, 2664, 2204, 1550, 1408. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*S*)-**10a**. MS (20 eV): *m*/*z* 131 (M^+), 89, 87, 70, 55, 41. HR-ESI-TOF: Calcd for $C_6H_{13}O_2N$ $[M+H]^+$: 132.10191; found: 132.10211.

4.8.3. 2(*S*)-([Amino]methyl)-4-methylpentanoic acid, (*S*)-10b

The general procedure was followed and the crude product was purified by flash chromatography using isopropyl alcohol–methanol–ammonium hydroxide (5:2:1) as eluent to give the desired product in 81% yield, mp 226–228 °C. $[\alpha]_D^{25} = -4$ (*c* 1.0, H_2O) for 94% ee, Chirobiotic T, MeOH–H_2O (80:20), 1 mL/min, 205 nm, *t* = 10.37 min. [Lit.[20] mp 219–220 °C, $[\alpha]_D^{25} = +6.1$]. IR (KBr, cm^{-1}): ν_{max} 3424, 2958, 2638, 2178, 1630, 1580, 1496. ^1H NMR (D_2O, 300 MHz) δ (ppm): 3.15–2.95 (m, 2H), 2.72–2.63 (m, 1H), 1.52–1.39 (m, 2H), 1.29–1.21 (m, 1H), 0.74–0.71 (dd, 6H, $J_1 = 5.9$, $J_2 = 3.7$ Hz). ^{13}C NMR (D_2O, 75.5 MHz) δ (ppm): 177.7, 41.4, 40.5, 25.4, 21.9, 21.7. MS (20 eV): *m*/*z* 146 (M^++H), 128, 102, 89, 73, 55, 43. HR-ESI-TOF: Calcd for $C_7H_{15}O_2N$ $[M+H]^+$: 146.11756; found: 146.11797.

4.8.4. 2(*R*)-([Amino]methyl)-4-methylpentanoic acid, (*R*)-10b

The general procedure was followed and the crude product was purified by flash chromatography using isopropyl alcohol–methanol–ammonium hydroxide (5:2:1) as eluent to give the desired product in 92% yield, mp 224–226 °C. $[\alpha]_D^{25} = +8$ (*c* 1.0, H_2O) for 99% ee, Chirobiotic T, MeOH–H_2O (80:20), 1 mL/min, 205 nm, *t* = 7.55 min. IR (KBr, cm^{-1}): ν_{max} 2958, 2638, 2178, 1630, 1582, 1496. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*S*)-**10b**. MS (20 eV): *m*/*z* 146 (M^++H), 128, 102, 89, 73, 55, 43. HR-ESI-TOF: Calcd for $C_7H_{15}O_2N$ $[M+H]^+$: 146.11756; found: 146.11780.

4.8.5. 2(*S*)-([Amino]methyl)-3-{1-[(*tert*-butoxy)carbonyl]-1*H*-indol-3-yl}propionic acid, (*S*)-10c

The general procedure was followed and the crude product was purified by silica flash chromatography using isopropyl alcohol–methanol–ammonium hydroxide (6:1:1) as eluent to give the desired product in 65% yield, mp 168–170 °C. $[\alpha]_D^{25} = +7.4$ (*c* 0.95, MeOH) for 82% ee, Chirobiotic T, MeOH–H_2O (80:20), 1 mL/min, 230 nm, *t* = 12.23 min. IR (KBr, cm^{-1}): ν_{max} 3428, 3108, 2972, 2932, 2360, 1728, 1580, 1452, 1256. ^1H NMR (D_2O, 400 MHz) δ (ppm): 7.55–7.21 (m, 2H), 7.16 (s, 1H), 6.92–6.87 (m, 2H), 3.04–2.92 (m, 3H), 2.80–2.61 (m, 2H), 1.26 (s, 9H), 1.09 (s, 1H). ^{13}C NMR (D_2O, 100.5 MHz) δ (ppm): 175.9, 150.6, 84.8, 42.9, 40.1, 27.6, 24.9. MS (20 eV): *m*/*z* 318 (M^+), 233, 201, 189, 156, 130, 117, 57, 41. HR-ESI-TOF: Calcd for $C_{17}H_{22}O_4N_2$ $[M+H]^+$: 319.16523; found: 319.16597.

4.8.6. 2(*R*)-([Amino]methyl)-3-{1-[(*tert*-butoxy)carbonyl]-1*H*-indol-3-yl}propionic acid, (*R*)-10c

The general procedure was followed and the crude product was purified by flash chromatography using isopropyl alcohol–methanol–ammonium hydroxide (6:1:1) as eluent to give the desired product in 81% yield, mp 160–162 °C. $[\alpha]_D^{25} = -5.9$ (*c* 1.19, MeOH) for 86% ee, Chirobiotic T, MeOH–H_2O (80:20), 1 mL/min, 230 nm, *t* = 9.10 min. IR (KBr, cm^{-1}): ν_{max} 3422, 2974, 2932, 2362, 1790, 1576, 1456, 1370, 1260. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*S*)-**10c**. MS (20 eV): *m*/*z* 318 (M^+), 233, 201, 189, 156, 130, 117, 57, 41. HR-ESI-TOF: Calcd for $C_{17}H_{22}O_4N_2$ $[M+H]^+$: 319.16523; found: 319.16597.

4.9. General procedure for the preparation of derivatives 11a–c

The corresponding amino acid (7.17 mmol, 1 equiv) was suspended in 0.15 M aqueous Na_2CO_3 (14.33 mmol, 2 equiv). The suspension was treated with a solution of Fmoc-OSu (8.6 mmol, 1.2 equiv) in acetone (95 mL) to obtain a homogeneous solution. The solution was stirred for 20 h at room temperature. The solvent was partially evaporated in vacuo and diluted with H_2O (20 mL) and Et_2O (100 mL). The aqueous phase was acidified to pH 2 with 1 M HCl and extracted with EtOAc (2 × 100 mL). The organic phases were combined, dried over anhydrous Na_2SO_4, and concentrated in vacuo.

4.9.1. 2(*S*)-[{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}methyl]-3-methylbutanoic acid, (*S*)-11a

The general procedure was followed and the crude product was purified by flash chromatography using methanol–dichloromethane (5:95) as eluent to give the desired product in 40% yield, mp 121–123 °C. $[\alpha]_D^{25} = +22$ (*c* 1.0, MeOH) for 99% ee, Chiralcel OD, *i*-PrOH–hexane–TFA; 10:90:0.1, 1 mL/min, 254 nm, *t* = 69.77 min; [Lit.[21] mp 112 °C, $[\alpha]_D^{25} = +11.5$ (*c* 0.97, $CHCl_3$)]. IR (KBr, cm^{-1}): ν_{max} 3342, 2964, 1700, 1542, 1448, 1268, 1140. ^1H NMR (CD_3OD, 400 MHz) δ (ppm): 0.95 (d, 3H, *J* = 6.8), 0.99 (d, 3H, *J* = 7), 1.88 (ddd, 1H, $J_1 \approx J_2 = 13.5$, $J_3 = 6.8$ Hz), 2.41 (m, 1H), 3.3 (m, 2H), 4.17 (m, 1H), 4.29 (m, 2H), 4.93 (s, 2H), 7.34 (m, 4H), 7.61 (d, 2H, *J* = 7.4), 7.75 (d, 2H, *J* = 7.4). ^{13}C NMR (CD_3OD, 100.5 MHz) δ (ppm): 19.0, 19.4, 28.5, 40.4, 40.5, 47.1, 66.5, 119.6, 124.98, 126.8, 127.4, 141.2, 144.0, 157.4, 176.3.

4.9.2. 2(*R*)-[{(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}methyl]-3-methylbutanoic acid, (*R*)-11a

The general procedure was followed and the crude product was purified by flash chromatography using methanol–dichloromethane

(5:95) as eluent to give the desired product in 41% yield, mp 121–123 °C. $[\alpha]_D^{25} = -23$ (*c* 1.0, MeOH) for 95% ee, Chiralcel OD, *i*-PrOH–hexane–TFA; 10:90:0.1, 1 mL/min, 254 nm, $t = 108.97$ min. [Lit.[22] $[\alpha]_D^{25} = -12.1$ (*c* 0.97, $CHCl_3$)]. IR (KBr, cm^{-1}): ν_{max} 3342, 2964, 1700, 1540, 1266. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*S*)-**11a**.

4.9.3. 2(*S*)-[{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}methyl]-4-methylpentanoic acid, (*S*)-11b

The general procedure was followed and the crude product was purified by flash chromatography using methanol–dichloromethane (5:95) as eluent to give the desired product in 41% yield, mp 138–140 °C. $[\alpha]_D^{25} = +11.6$ (*c* 0.6, MeOH) for 96% ee, Chiralcel OD, *i*-PrOH–hexane–TFA; 10:90:0.1, 1 mL/min, 254 nm, $t = 69.75$ min. [Lit.[21] mp 134 °C, $[\alpha]_D^{25} = +10.8$ (*c* 0.6, $CHCl_3$)]. IR (KBr, cm^{-1}): ν_{max} 3066, 2956, 1550, 1448, 1370, 1164, 1010. ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 10.6 (br s, 1H), 7.77–7.31 (m, 8H), 5.3 (br s, 1H), 4.51–4.22 (m, 3H), 3.47–3.12 (m, 2H), 2.76–2.65 (m, 1H), 1.74–1.22 (m, 3H), 0.95 (d, 6H, $J = 4.4$ Hz). ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ (ppm): 180.8, 156.6, 144.0, 127.8, 127.2, 125.2, 120.1, 66.9, 47.3, 43.8, 42.3, 38.6, 25.9, 22.6.

4.9.4. 2(*R*)-[{[(9*H*-Fluoren-9-ylmethoxy)carbonyl]amino}methyl]-4-methylpentanoic acid, (*R*)-11b

The general procedure was followed and the crude product was purified by flash chromatography using methanol–dichloromethane (5:95) to give the desired product in 46% yield, mp 134–135 °C. $[\alpha]_D^{25} = -8.3$ (*c* 0.6, MeOH) for 99% ee, Chiralcel OD, *i*-PrOH–hexane–TFA; 10:90:0.1, 1 mL/min, 254 nm, $t = 129.72$ min. IR (KBr, cm^{-1}): ν_{max} 3066, 2956, 1448, 1368, 1164, 1082. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*S*)-**11b**.

4.9.5. (*S*)-3-({[(Fluoren-9-yl)methoxy]carbonyl}amino)-2-({1-([*tert*-butoxy]carbonyl)-1*H*-indol-3-yl}methyl)propionic acid, (*S*)-11c

The general procedure was followed and the crude product was purified by flash chromatography using methanol–dichloromethane (5:95) as eluent to give the desired product in 65% yield, mp 128–130 °C. $[\alpha]_D^{25} = +12.5$ (*c* 1, $CHCl_3$) for 90% ee, Chiralcel OD-H, *i*-PrOH–hexane–TFA; 20:80:0.1, 1 mL/min, 210 nm, $t = 24.8$ min. [Lit.[6c] mp 125–128 °C. $[\alpha]_D^{25} = -5.0$ (*c* 1.04, $CHCl_3$) for the enantiomer]. IR (KBr, cm^{-1}): ν_{max} 3340, 3062, 2978, 2928, 2360, 1550, 1728, 1606, 1452, 1372, 1256, 1158, 1090, 856. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.07 (d, 1H, $J = 7.9$ Hz), 7.71 (d, 2H, $J = 7.3$ Hz), 7.59–7.43 (m, 4H), 7.34–7.14 (m, 6H), 4.9 (s, 2H), 4.28 (d, 2H, $J = 6.8$ Hz), 4.12 (t, 1H, $J = 6.7$ Hz), 3.47–3.25 (m, 2H), 3.05–2.74 (m, 3H), 1.61 (s, 9H). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (ppm): 157.9, 150.1, 144.2, 141.5, 135.8, 130.8, 127.7, 127.1, 125.2, 124.4, 123.5, 122.6, 119.9, 119.1, 118.5, 115.1, 83.6, 66.8, 47.4, 42.7, 27.4, 26.9, 25.2.

4.9.6. (*R*)-3-({[(Fluoren-9-yl)methoxy]carbonyl}amino)-2-({1-([*tert*-butoxy]carbonyl)-1*H*-indol-3-yl}methyl)propionic acid, (*R*)-11c

The general procedure was followed and the crude product was purified by flash chromatography using methanol–dichloromethane (5:95) as eluent to give the desired product in 58% yield, mp 128–130 °C. $[\alpha]_D^{25} = -18.5$ (*c* 1, $CHCl_3$) for 88% ee, Chiralcel OD-H, *i*-PrOH–hexane–TFA; 20:80:0.1, 1 mL/min, 210 nm, $t = 40.38$ min. IR (KBr, cm^{-1}): ν_{max} 3410, 2974, 2934, 2360, 1724, 1574, 1450, 1374, 1258, 1158, 1090, 856. The ^1H and ^{13}C NMR data were identical to those recorded in enantiomeric (*S*)-**11c**.

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